# Photocleavage of Benzyl–Sulfide Bonds

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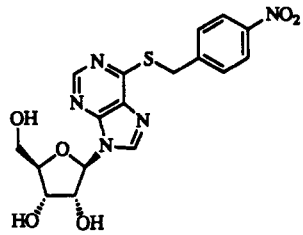
The nucleoside transport inhibitor 6-[(4-nitrobenzyl)thio]-9-(β-D-ribofuranosyl)purine, NBMPR, has been used successfully in photoaffinity labeling. We have studied the mechanism for photocleavage of the benzyl–sulfur bond by using substituted benzyl phenyl sulfides as analogues of NBMPR. This has enabled us to enhance the photoreactivity of the benzyl–sulfur bond. We have also performed "radical clock" studies with a hexenyl side chain to trap reactive intermediates. The mechanistic interpretation from the substituent and side chain studies is that the benzyl–sulfur moiety is photocleaved via a homolytic pathway.

Recently, we reported the photochemical reactivity of the ribonucleoside 6-[(4-nitrobenzyl)thio]-9-(β-D-ribofuranosyl)purine, NBMPR (1).[1] There was interest in the



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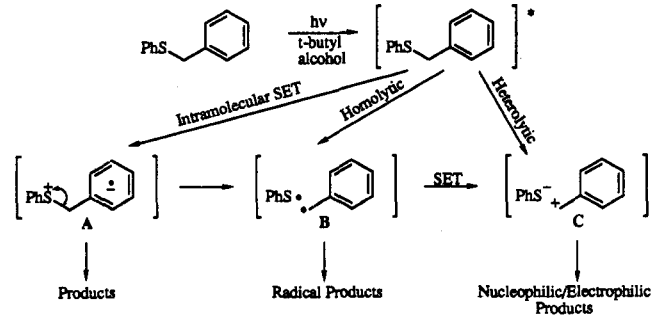
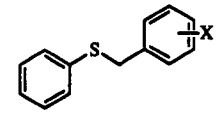
photochemistry of 1 due to its successful photoaffinity labeling of a membrane transport protein.[2] We were intrigued by the possibility of further applications in photoaffinity labeling with the photoactive group of 1. In our earlier study,[1] we found that the active site in the photolysis of 1 is the benzyl–sulfur bond, and the primary pathway is cleavage of this moiety. Other research groups have studied similar benzyl–heteroatom photocleavage reactions.[3] Photocleavage of the benzyl–sulfur bond is well known,[4] but the nature of the photochemical bond-breaking process has not been extensively examined nor is there literature available on the effect that substituents have in this reaction. In this paper, we examine the mechanism of benzyl–sulfur bond cleavage, and while doing so we report substituent studies that will prove useful in the development of new photoaffinity labeling reagents.

Possible cleavage mechanisms include those shown in Scheme I. Three intermediates are shown as potentially arising from the initial excited state: **A** arises from intramolecular SET, **B** from homolytic cleavage, and **C** from heterolytic cleavage.[5] Presumably, any combination of these pathways could occur.

**Scheme I**




The methods employed to study these potential mechanisms were as follows: (1) analysis of photoproducts formed in the irradiation of benzyl phenyl sulfide (BPS, **2**) and several *p*- and *m*-benzyl substituted derivatives (**3a–7b**), (2) a radical-trapping investigation using 6-phenylthio)-6-phenyl-1-hexene (**8**) to trap **B**, and (3) analysis of the Weller equation and UV experiments in order to determine the presence of **A**.



| | | | |
|---|---|---|---|
| **2** | X = H | | |
| **3a** | *p*$OCH_3$ | **3b** | *m*$OCH_3$ |
| **4a** | *p*$CH_3$ | **4b** | *m*$CH_3$ |
| **5a** | *p*$CF_3$ | **5b** | *m*$CF_3$ |
| **6a** | *p*CN | **6b** | *m*CN |
| **7a** | *p*$NO_2$ | **7b** | *m*$NO_2$ |

## Results and Discussion

Major photoproducts[6] for the photolysis of compounds **2–7** are shown in Scheme II. Photoproducts diphenyl disulfide and the substituted bibenzyls are most likely the result of radical coupling. Diphenyl sulfide is a secondary photoproduct from diphenyl disulfide as we have previously shown.[1] The substituted toluenes presumably arise via hydrogen atom abstraction by the benzyl

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(1) (a) Fleming, S. A.; Rawlins, D. B.; Robins, M. J. *Tetrahedron Lett.* **1990**, *31*, 4995. (b) Fleming, S. A.; Rawlins, D. B.; Samano, V.; Robins, M. J. *J. Org. Chem.* **1992**, *57*, 5968.

(2) Young, J. D.; Jarvis, S. M.; Robins, M. J.; Paterson, A. R. P. *J. Biol. Chem.* **1983**, *258*, 2202.

(3) (a) Zimmerman, H. E.; Sandel, V. R. *J. Am. Chem. Soc.* **1963**, *85*, 915. (b) Givens, R. S.; Matuszewski, B.; Athey, P.; Stoner, M. R. *J. Am. Chem. Soc.* **1990**, *112*, 6016. (c) Foster, B.; Gaillard, B.; Mathur, A.; Pincock, A. L.; Pincock, J. A.; Sehmbey, C. *Can. J. Chem.* **1987**, *65*, 1599. (d) Breslin, D. T.; Saeva, F. D. *J. Org. Chem.* **1988**, *53*, 713. (e) Bartl, J.; Steenken, S.; Mayr, H.; McClelland, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 6918. (f) Cristol, S. J.; Bindel, T. H. *J. Org. Chem.* **1980**, *45*, 951. (g) Penn, J. H.; Lin, Z. *J. Org. Chem.* **1990**, *55*, 1554. (h) Stock, L. M.; Cheng, C. *J. Org. Chem.* **1991**, *56*, 2436.

(4) (a) Bastein, G.; Surzur, J. M. *Bull. Soc. Chim. Fr.* **1979**, 601. (b) Reid, S. T. In *Photochemistry*; Bryce-Smith, D., Ed.; Burlington House: London, 1983-1988; Part III, Vols. 13–19, Chapter 7.

(5) On the basis of product analysis in our previous study[1] we concluded that heterolytic cleavage did not occur via the benzyl anion.

(6) Most of the major photoproducts are readily available in our laboratory which has allowed for the confirmation of their presence in the photomixture. Available photoproducts include the following: bibenzyl, diphenyl disulfide, diphenyl sulfide, toluene and substituted toluenes, benzaldehydes, and diphenylmethane. Analysis is based on major (ca. > 2%) photoproducts.

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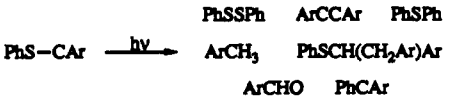
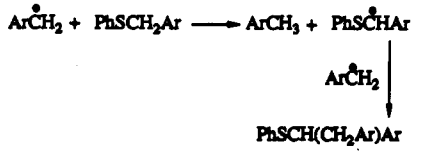
**Scheme II**




**Scheme III**

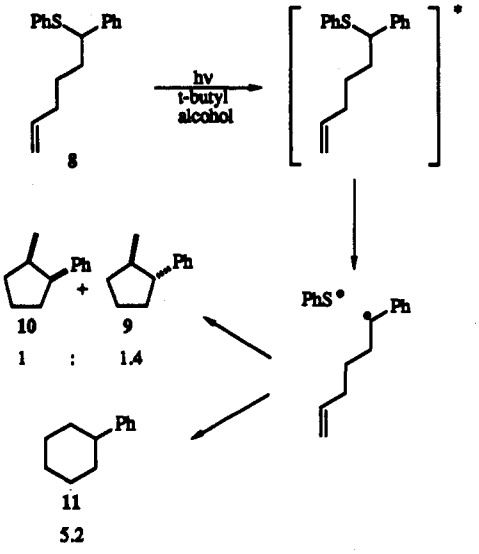



radical from the benzyl position of the starting material which leads to subsequent formation of the 1,2-diaryl 1-phenyl thioethers (see Scheme III). Although there are several possible pathways that could lead to the substituted benzaldehydes, we suspect that dissolved oxygen reacts with the radical intermediate. The phenylarylmethanes are formed from desulfurization of starting materials.[7] No products resulting from heterolytic cleavage (such as thiophenol or benzyl ethers) were detected.

The rate of cleavage for each of the substituted benzyl phenyl sulfides was also measured qualitatively[8] in order to determine potential utility for photoaffinity labeling. The results from the irradiation of these substituted derivatives show that the *m*-(trifluoromethyl)benzyl sulfide is the most effective photocleaving reagent and would have potential as the photoactive group in a photoaffinity label.[9]

In an attempt to trap **B**, we synthesized and irradiated 8 (see Scheme IV). If the benzyl radical formed in the photolysis of 8 has sufficient lifetime it would undergo intramolecular cyclization to give 1-methyl-2-phenylcyclopentane,[10] a product that would not be formed from a benzyl cation intermediate. We found that upon photolysis of 8 benzyl radical intermediates are trapped by cyclization to give three ring-closed products: *trans*-1-methyl-2-phenylcyclopentane (**9**), *cis*-1-methyl-2-phenylcyclopentane (**10**), and phenylcyclohexane (**11**).[11] The overall yield of ring-closed products was only 7.0%; however, the major photoproducts formed (6-phenyl-1-hexene and 1-phenyl-1,5-hexadiene) also arise from a radical intermediate. Ratios as shown in Scheme IV compare reasonably well with similar examples of ring closure in homolytic pathways.[12] When methanol is used

**Scheme IV**




as a solvent, no ether product (resulting from attack of the oxygen onto a benzyl or cyclohexyl cation) was observed.

The observed competitive intramolecular trapping of the radical intermediate allows us to conclude that its lifetime[13] is at least $10^{-6}$ s. We have found that there is a solvent dependency on the trapping process, and we expect that back-reaction of the radical pair in its solvent cage is the competing process.

Analysis of the Weller equation[14] with literature values for electron transfer[15] suggests that initial electron transfer between these moieties is energetically favorable[16] and cannot be precluded a priori. To test for the presence of **A** we examined the UV spectra of thioanisole, *p*-nitrotoluene, and a mixture of the two. Since no shift was observed in the mixture, and the *p*-nitrotoluene radical anion[17] ($\lambda_{max}$ = 330 nm) was not observed, **A** is presumably not present is significant amounts.

## Conclusion

Our results indicate that the major pathway for photocleavage of the benzyl–sulfide bond is the homolytic route. Photoproduct analysis indicates that radical products are the major results of photolysis. We successfully trapped the radical intermediate **B** with a "radical clock", and spectroscopic analysis shows that intramolecular SET does not occur to any significant extent. We also found that the *m*-(trifluoromethyl)benzyl sulfide is an effective photocleaving reagent and may have potential as the photoactive group for photoaffinity labeling.

## Experimental Section

**General Procedures.** Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. Dimethylformamide and *tert*-butyl alcohol were distilled over $CaH_2$. All reactions were performed under argon or dry nitrogen. NMR spectra were obtained on a 200-MHz instrument. Microanalyses were performed by M-H-W Laboratories. Benzyl phenyl sulfide

(7) Kropp, P. J.; Fryxell, G. E.; Tubergen, M. W.; Hager, M. W.; Harris, G. D.; McDermott, T. P.; Tornero-Velez, R. *J. Am. Chem. Soc.* **1991**, *113*, 7300.

(8) The rate for loss of starting material was measured by following the reaction with GC.

(9) When all of the relative rates were compared, *m*-$CF_3$ was considerably faster than all others. We attempted to fit our relative rate data to $\sigma$ values in order to obtain Hammett plots, which would give us more mechanistic information. Only the para-substituted compounds showed correlation. They gave a slightly positive slope when fit to $\sigma^+$ values ($\rho$ = 0.28). However, these rate studies are only qualitative, and definite conclusions with respect to Hammett plots should not be made without quantum yields and further studies to determine the reaction multiplicity of each derivative. We found that the order for rate of disappearance for meta-substituted derivatives is *m*-$CF_3$ > *m*-$OCH_3$ > *m*-CN > *m*-$CH_3$ > -H > *m*-$NO_2$. This trend does not correlate well with any $\sigma$ values; perhaps due to the "meta effect".[3a] We are continuing to investigate these intriguing results.

(10) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; deMayo, P., Ed.; Academic: New York, 1980; Vol. 1, Essay 4, pp 185–198.

(11) Product analysis was performed by coinjection of independently synthesized products with the photomixture and internal standard using GC. GCMS and NMR were also used to identify photoproducts.

(12) Givens, R. S.; Singh, R. *Tetrahedron Lett.* **1991**, *32*, 7013.

(13) (a) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739. (b) Newcomb, M.; Curran, D. P. *Acc. Chem. Res.* **1988**, *21*, 206.

(14) Kavarnos, G. J.; Turro, N. J. *Chem. Rev.* **1986**, *86*, 401.

(15) (a) Berkessel, A. *Bioorg. Chem.* **1991**, *19*, 101. (b) Lawless, G.; Bartak, D. E.; Hawley, M. D. *J. Am. Chem. Soc.* **1969**, *91*, 7121.

(16) The calculated $\Delta G$ value for electron transfer is −49 kcal/mol.

(17) (a) Buncel, E.; Menon, B. C. *J. Am. Chem. Soc.* **1980**, *102*, 3499. (b) Shida, T.; Iwata, S. *J. Phys. Chem.* **1971**, *75*, 2591.

was purchased from Lancaster and used without further purification. The known compounds **3a**, **4a**, **4b**, **5a**, **6a**, **6b**, **7a**, and **7b** were synthesized using standard procedures.

**3-Methoxybenzyl Phenyl Sulfide (3b).** To 1.0 equiv of thiophenol in distilled dimethylformamide was added 1.2 equiv of 3-methoxybenzyl chloride and 1.2 equiv of potassium carbonate. This slurry was stirred at room temperature for 24 h under inert atmosphere. The solution was transferred into aqueous sodium bicarbonate and ether; the organic layer was washed with brine and water and then dried over anhydrous sodium sulfate. Concentration in vacuo gave crude material (94%) that was distilled to give a colorless oil with bp 142 °C/0.2 Torr. Spectral data were as follows: NMR ($CDCl_3$) $\delta$ 6.7–7.4 (m, 9 H, arom), 4.05 (s, 2 H), 3.70 (s, 3 H, methoxy); IR (neat) 1231, 1047, 780, 690 $cm^{-1}$; UV (95% EtOH) $\lambda_{max}$ 261 (12 000). Anal. Calcd for $C_{14}H_{14}OS$: C, 73.01; H, 6.13; S, 13.92. Found: C, 72.86; H, 6.00; S, 14.12.

**3-(Trifluoromethyl)benzyl Phenyl Sulfide (5b).** The procedure described above using $\alpha'$-chloro-$\alpha,\alpha,\alpha$-trifluoro-*m*-xylene gave crude yield of 64%. The oil was distilled at 150 °C/0.2 Torr. Spectral data were as follows: NMR ($CDCl_3$) $\delta$ 7.1–7.6 (m, 9 H, arom), 4.10 (s, 2 H); IR (neat) 810, 700, 690, 670 $cm^{-1}$; UV (95% EtOH) $\lambda_{max}$ 255 (8600). Anal. Calcd for $C_{14}H_{11}F_3S$: C, 65.38; H, 4.31; S, 12.47. Found: C, 65.28; H, 4.45; S, 12.70.

**6-(Phenylthio)-6-phenyl-1-hexene (8).** To 0.881 g (4.41 mmol) of benzyl phenyl sulfide dissolved in 25 mL of THF at −78 °C was added 1.1 equiv of nBuLi. The mixture was stirred for 0.5 h at −78 °C, and then 0.640 mL (5.40 mmol) of 5-bromo-1-pentane was added dropwise. The reaction was allowed to warm to rt and stirred for 12 h. The reaction was quenched with water and ether extracted. The ether layers were washed with aqueous sodium bicarbonate, water, and brine and then dried over anhydrous sodium sulfate. Distillation at 175 °C/0.1 Torr gave colorless oil in 80% yield. The spectral data were as follows: NMR ($CDCl_3$) $\delta$ 7.1–7.3 (m, 10 H, arom), 5.71 (m, 1 H) 4.94 (m, 2 H), 4.10 (m, 1 H), 1.98 (m, 4 H), 1.42 (m, 2 H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 142.6, 138.8, 135.6, 132.8, 129.1, 128.8, 128.3, 127.5, 127.4, 115.3, 54.0, 36.2, 33.9, 27.3. Anal. Calcd for $C_{18}H_{20}S$: C, 80.54; H, 7.51; S, 11.95. Found: C, 80.54; H, 7.42; S, 12.17.

**General Photolysis Procedures.** Irradiations were performed using a Hanovia 450-W medium-pressure Hg lamp in a water-cooled quartz well with the samples in quartz test tubes at a 1.5-cm distance from the well. The samples were dissolved in freshly distilled *tert*-butyl alcohol and deoxygenated prior to photolysis with purified nitrogen[18] gas bubbled through the solutions for 30 min. Photolysis concentrations of benzyl phenyl sulfide and its derivatives (**2**–**7b**) for the Hammett plot study were $10^{-2}$ M. The concentration of the alkene (**8**) in the radical clock study was $10^{-3}$ M. Samples were removed from the photolysis, spiked with benzophenone, and immediately analyzed by gas chromatography.

(18) Nitrogen was purified by passing it through an Ace-Burlitch inert atmosphere system containing a column packed with a BASF R3-11 catalyst followed by another column packed with Aquasorb drying agent.